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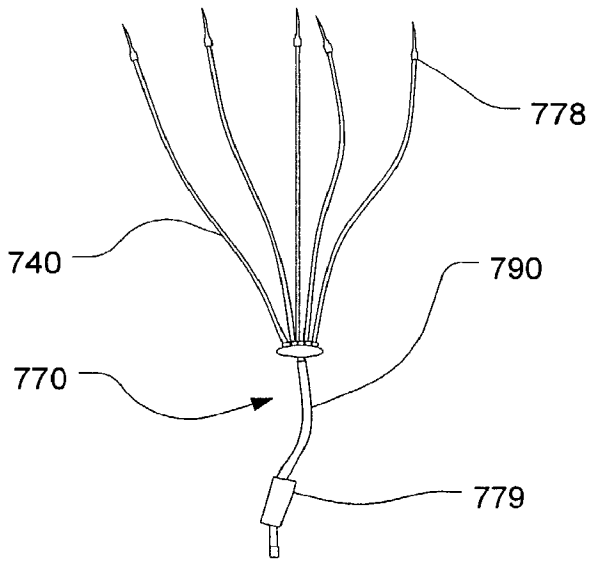
(54) Title: LAST-CHANCE QUALITY CHECK AND/OR AIR/PYROGEN FILTER FOR INFUSION SYSTEMS



(57) Abstract: Blood treatment system and method for high rate hemofiltration ensures against pyrogenic patient reaction by providing various mechanisms for filtering replacement fluid to remove endotoxins and other safety features including detecting incorrect fluid administration.

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S P E C I F I C A T I O N

LAST-CHANCE QUALITY CHECK AND/OR AIR/PYROGEN FILTER FOR INFUSION SYSTEMS

Background of the Invention

During hemofiltration, hemodialysis, hemodiafiltration, ultrafiltration, and other forms of renal replacement therapy, blood is drawn from a patient, passed through a filter, and returned to the patient. Depending on the type of treatment, fluids and electrolytes are exchanged in the filter between a dialysate and/or extracted from the blood by filtration. One effect may be a net loss of fluid and electrolytes from the patient and/or exhaustion of dialysate, with a concomitant need for its replenishment, again depending on the type of treatment. To replace fluid lost from the patient and keep the patient from dehydrating, replacement fluid may be injected into the patient at a rate that matches a rate of loss, with an adjustment for a desired net change in the patient's fluid complement. To replace exhausted dialysate, fresh dialysate is continuously circulated through the filter.

Presently methods to produce large volumes of dialysate from tap water are known, but each requires complex water purification and standardization equipment, since impurities and cleaning additives such as chlorine vary greatly in tap water from municipality to municipality and within a municipality over time. (See Twardowski U.S. Patent Nos. 6,146,536 and 6,132,616.)

Moreover, dialysate solution, whether prepared online or prepackaged, while of the proper concentration for use as a replacement fluid, is not directly infused into the patient's body. Instead, dialysate flows past a semipermeable membrane that permits ions and water to be exchanged across the membrane until a balance between their concentrations in blood and their concentrations in the dialysis is achieved. This is effective to remove impurities from the blood and to add missing electrolytes to the blood, but the volume of fluid that is infused is not as great as with hemofiltration.

Conventionally, dialysate and/or replacement fluid is supplied from either of two sources: batches of fluid, typically in multiple bags, or a continuous sources of water that is sterile-filtered and added to concentrated electrolytes to achieve the required dilution level. Because replacement fluid is injected directly into the patient, replacement fluid is required to be sterile and is recommended to have limited levels of pyrogens, particularly endotoxins, which are quantified in endotoxin units (EU). The maximum amount of endotoxin allowed in a parenteral product or medical device set by the US Food and Drug Administration (FDA) and United States Pharmacopoeia (USP) for drugs is 5.0 EU/Kg/hr, a rate taking into account the weight of the patient (in Kg.) and the rate of infusion. Currently, however, replacement fluid packaged such that it is regulated as a drug may have an endotoxin load of up to 0.5 EU/ml. This would limit the replacement fluid exchange rate for a 72 Kg. patient to less than 12 ml./min. To be

safely infused, per these specifications, at higher rates, the fluid must be further filtered of endotoxins. Filtering to 0.03 EU/ml., a level that may be identified as "ultrapure," allows an infusion rate of 200 ml./min., which may be sufficient for high rate continuous hemofiltration therapy of the type described in the following pending US patent applications each of which is hereby incorporated by reference as fully set forth in its entirety herein.

08/800,881, filed Feb. 14, 1997 for Hemofiltration System;

09/451,238 for Nov. 29, 1999 for Systems and Methods for Performing Frequent Hemofiltration;

09/512,929, filed Feb. 25, 2000 for Fluid Replacement systems & Methods for Use in Hemofiltration;

09/513,564, filed Feb. 25, 2000 for Systems and Methods for Detecting Air in an Arterial Blood Line of a Blood Processing Circuit;

60/438,567, filed Jan. 30, 2003 for Preparing Replacement Fluid by Means of Batch Filtration Prior to Treatment;

09/513,910, filed Feb. 25, 2000 for Systems and Methods that Maintain Sterile Extracorporeal Processing Conditions;

09/513,911, filed Feb. 25, 2000 for Synchronized Volumetric Fluid Balancing Systems and Methods;

09/513,915, filed Feb. 25, 2000 for Systems and Methods for Controlling Blood Flow & Waste Fluid Removal During Hemofiltration;

09/862,207, filed May 21, 2001 for Methods, Systems and Kits for the Extracorporeal Processing of Blood;

09/865,905, filed May 24, 2001 for Fluid Processing Systems and Methods Using Extracorporeal Fluid Flow Panels Oriented Within a Cartridge;

09/894,236, filed June 27, 2001 for Hemofiltration System;

09/900,362, filed July 7, 2001 for Method and Apparatus for Leak Detection in a Fluid Line (Disconnect Sensor - Reverse Lines to Use Air Sensor on Arterial Line (Leak));

09/905,246, filed July 12, 2001 for Devices and Methods for Sterile Filtering;

09/907,872, filed July 17, 2001 for Hermetic Flow Selector Valve;

60/324,437 filed Sept. 24, 2001 for Device and Method for Enhancing Performance of Membranes.

10/040,659, filed January 7, 2002 for Blood Treatment Replacement Fluid Using Infusible Fluids in Combination;

60/346,458 filed January 7, 2002 for Hemofiltration Filter with High Membrane Utilization Effectiveness; and

60/346,403 filed January 7, 2002 for Hemofiltration System Method of Use and Associated Control System.

In many instances, blood treatment therapies may require a large quantity of sterile fluid. A typical way to provide the large quantity of replacement fluid is to provide multiple bags of replacement fluid, dialysate, or infusate. The connection of these bags of fluid to an extracorporeal blood circuit creates a risk of touch contamination resulting in the introduction of contaminants into the fluids. Contamination may occur, for example, at the point where bags of fluid

are accessed ("spiked") or at other times during preparation for infusion such as when the patient is accessed.

Attempts to render dialysate suitable for use as a replacement fluid in hemofiltration and hemodiafiltration have focused on continuous sterilization processes that require a separate dialysate filtration / purification apparatus that must be periodically purged and verified to provide sufficient constant flow of sterile replacement fluid required for hemofiltration. (See Chavallet U.S Patent Nos. 6,039,877 and 5,702,597.) Such devices are necessarily complicated and require separate pumping systems for the sterilization process. In addition, the rate of supply of dialysate for such systems is very high, requiring an expensive filter to be used. The same high-rate problem exists for the generation of replacement fluid for hemofiltration, and therefore also requires an expensive filter.

There is a need for improved mechanisms for providing safe economic replacement fluid for use in various blood therapies.

Summary of the Invention

In the present invention, sterile, and preferably substantially non-pyrogenic (e.g., including endotoxin-free) replacement fluid or dialysate may be generated in batch form by filtering. According to various embodiments of inventions disclosed,

1. raw fluid is passed through a filter prior to treatment to prepare a batch of infusible replacement fluid;
2. raw fluid is passed by gravity feed during treatment through filters attached to infusion lines from each of one or more batch containers;
3. raw or prefiltered fluid according to either or both of the previous methods is passed through a last-chance filter immediately prior to injection into the patient.

Preferably, the filter has a pore size and quality effective to block endotoxins such that the replacement ultimately infused that is substantially less than 5 EU/Kg./hr (based on the rate of treatment), the limit set by the USP for parenteral drugs and no more than 0.5 EU/ml. Preferably the filter provides this degree of filtration with minimal pressure drop, for example by means of a relatively large pore size (e.g., 02. Micron) in combination with a charged nylon membrane which attracts endotoxins and helps to ensure against their passage. Filters are available with smaller pore sizes and may be used rather than relying on adsorption as with the nylon membrane example. For example pores sizes of 0.005 micron and somewhat larger will block most endotoxins. But small pore

size implies high pressure drop and generates inefficiencies for production.

The raw (source) replacement fluid may be industry standard quantities of pyrogens and labeled as suitable for injection, the inventive method providing a higher degree of purity than is currently allowed for infusible fluids regulated either as medical devices or drugs.

The batch filtration process may be permitted to take any length of time because the rate of flow of raw replacement fluid (or components thereof) through the filter is completely independent of the rate of consumption by the renal therapy. Because the filters used for such filtering tend to be expensive, it may be desirable for such a batch process to employ a small pyrogen filter for such filtration. Such a filter can have a flow capacity that is much lower than that required for real-time filtering of the replacement fluid (or components). Alternatively, the fluid may be passed under pressure for a suitably supported membrane or strong membrane material adequate to permit real-time filtration as discussed elsewhere in the present specification. In addition to preparation of low pyrogen (preferably at least with low levels of endotoxins) fluid from sterile or non-sterile and/or pyrogen-purified fluid, embodiments of inventions disclosed may be used to ensure against touch contamination.

Treatment by hemofiltration requires the extraction from patients of a large volume of fluid compared to hemodialysis, although both perform similar functions. In hemodialysis, fluid and electrolytes cross a filter membrane into and out of

the blood of the patient in response to a difference in concentration of electrolytes. Some net quantity of fluid may be taken from the patient if there is an excess in the patient's blood and some net quantity of replacement fluid may be infused directly if there is a paucity in the patient's blood. In hemofiltration, fluid is drawn out of the patient continuously and replaced with electrolytically-proper fluid. As a result, the quantity of fluid infused in the patient tends to be much greater than with hemodialysis and, coincidentally, most other types of infusion therapies including parental infusion therapies. In addition, new hemofiltration therapies have been developed which permit very fast continuous treatment, which may involve the infusion of replacement fluid at a very high rate. The risk of adverse reactions due to the infusion of pyrogens into patients increases with the dose and the period of time over which the infusion takes place. As a consequence, the allowed concentration of pyrogens in replacement fluid for hemofiltration should be substantially lower than for other treatments, for example for hemodialysis or other infusion therapies.

While low pyrogen levels may be achieved using sterilization and filtration techniques that are known, there are also a number of practical matters that are well to combine in addressing the problem of pyrogen infusion in hemofiltration. For example, even when highly purified replacement fluid is used for replacement fluid, touch-contamination can cancel any benefit of starting with a highly purified fluid.

In disclosed embodiments of blood treatments systems, including hemofiltration systems generally as well as high flow-rate hemofiltration systems particularly, the low pyrogen concentrations may be achieved by one or more features, including:

1. batch filtration of raw replacement fluid at the site of use and in a manner that minimizes risk of touch-contamination or other sources of recontamination;

2. filtration of raw replacement fluid at the site of use at the rate of consumption in real time during treatment, preferably with a filter located close to the point of injection so as to minimize the risk of downstream contamination;

3. filtration using filters that permit the passage of no more than 0.03 endotoxin units per ml.; and

4. filtration using filters using a combination of adsorption and blocking mechanisms to provide an optimal balance between pressure drop across the filter media and the need to block pyrogen particles, preferably with a charged nylon membrane, which attracts endotoxins thereby helping to block them and having an approximately 0.2 micron pore size.

Generally replacement fluid is heated before being infused into a patient. This is often accomplished by passing the fluid through a heater with enough heating capacity to heat the fluid as it is being infused. The capacity of the heater must be matched to the mass flow of the fluid and the temperature rise required. In a batch preparation process, where a batch of fluid is prepared over a substantial period before use, a small heater may

heat the replacement fluid over a long period of time. Insulation may be provided to prevent heat loss. An insulating outer container for the source replacement fluid may be provided. For example, the container may be an insulated box with room for one or more large disposable sterile bags of the type normally used for infusible fluids.

The preparation of warm replacement fluid may be automated by a control process that permits a user to set up the fluids and other materials well in advance of a scheduled treatment. The process would ensure that the replacement fluid is treated to remove pyrogens and heated to the proper temperature when the treatment is to begin. The automation process may be permit the user to select how far in advance of the treatment the preparation should be performed. This may be useful, for example, where a particular source of replacement fluid has proved to release more than a usual quantity of dissolved gases upon heating. Heating the replacement fluid and permitting it to settle for a time before it is used may allow gases to come out of solution and settle at the top of the batch vessel or vessels. The automation process may be incorporated in the control functions of renal therapy machine.

The invention or inventions will be described in connection with certain preferred embodiments, with reference to the following illustrative figures so that it may be more fully understood. With reference to the figures, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present

invention or inventions only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention or inventions. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention or inventions, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention or inventions may be embodied in practice.

Brief Description of the Drawings

Fig. 1 is a schematic illustration of a standalone/retrofit apparatus system for batch filtration of a sterile, endotoxin-purified, or pyrogen-purified replacement fluid.

Fig. 2 is a flow chart illustrating an exemplary control procedure applicable to various embodiments of the invention including those of Figs. 1 and 3.

Fig. 3 is a schematic illustration of a blood treatment machine with an attached subsystem for batch preparation of infusible replacement fluid.

Figs. 4A and 4B are illustrations of fluid filters that may be use in various embodiments of the invention.

Fig. 5 illustrates an exemplary blood treatment system with a filter used to filter gas, pyrogens, endotoxins, or pyrogens from replacement fluid during treatment.

Figs. 6-8 illustrate a blood treatment machine and cartridge providing various supporting mechanical features for the embodiment of Fig. 5 and further embodiments, including one in which a quality of replacement fluid is sensed before infusion.

Fig. 9 illustrates a disposable fluid circuit kit which may support various embodiments of the invention.

Fig. 10 illustrates a set up for priming a blood treatment process, which components of the invention may be used to support.

Fig. 11 illustrates a portion of a blood treatment machine that allows a pump used as part of

the blood treatment to also be used to control the filtering of fluid to provide a batch of infusible replacement fluid.

Fig. 12 illustrates a patient undergoing treatment.

Figs. 13 and 14 illustrate embodiments of a filtering manifold for filtering of infusible fluids.

Detailed Description

Referring to Fig. 1, a filter 160 filters fluid from a source of fluid 150 to generate a batch of infusible replacement fluid 130. The filter 160 may be, and preferably is, a microporous filter that blocks pyrogens and allows the passage of dissolved electrolytes and water. The latter may provide an infusible fluid free of all pyrogens, however, in practice, the pyrogen concentration must be reduced, but not necessarily eliminated since total elimination is not practical. The most common type of pyrogen is endotoxins, which may be present even in sterilized fluids.

In hemofiltration, a large quantity of fluid is drawn from the patient and replaced with replacement fluid. Compared to dialysis, the quantity actually removed and replaced with replacement fluid tends to be high. As a consequence, it is desirable to provide replacement fluid that has a lower concentration of pyrogens than may be allowed in other infusible fluids and what may cross the membrane of a dialysis system. Thus, a filter effective to reduce endotoxins to levels at least as low as 0.03 endotoxin units per ml. should be provided for the filter 160.

The result of the filtration process is the sterilization and cleansing of endotoxins and particulate pyrogens in the raw fluid from the source of fluid 150. The source of fluid 150 may be a container 196 of fluid approved for injection or non-sterile replacement fluid. It may also be one or more containers of constituents which, when combined, form a proper replacement fluid (not

shown) or a continuous source such as a tap water that is combined or has been combined with electrolyte concentrate (not shown). The starting fluid may be a function of the type of filter 160 used. For example, when processing fluid with a relatively large concentration of particulate pyrogens, for example bacteria, it is desirable to use a very large filter to ensure that its filtering performance is not compromised. In a preferred embodiment, a small replacement filter is used (since they tend to be costly) and the source fluid is fluid that has already been filtered to achieve low levels of pyrogens.

One or more conduit elements form a line 120 to convey the source fluid 150 through the filter 160 and into a batch container 147. The latter may be any type of sterile, preferably disposable container, for example, a large IV bag. It may also include a number of such containers appropriately interconnected to permit flow into and out of them in the fashion of container 147.

Included in the conveyance from source fluid 150 to infusible replacement fluid 130 may be a pump 190, such as a peristaltic pump. The pressure at an outlet of the filter 160 may be sensed by a pressure sensor 162 and the pump 190 controlled by a controller 170 to insure a predefined transmembrane pressure (TMP) threshold of the filter 160 is not breached. The TMP may be maintained at a maximum safe level to maximize throughput. Note that complexity may be avoided if the source fluid 150 is arranged such as to maintain a desired TMP at the filter 160 without the need of a pump 190 or pressure sensor 162. For example, the

source fluid 150 may be provided by a batch container elevated at a certain height to provide a desired head. Note that a control valve 165 or a speed of the pump 190 may be used to regulate the flow rate to maintain desired TMP limits.

A control/shutoff valve 180 may provide the controller 170 the ability to stop the flow of fluid through the filter 160 once a desired volume is reached. A heater 185 may be provided to warm the filtered replacement fluid 130 to prepare it for use. An insulated container 145 may be used to reduce heat loss so that heater 185 can be a relatively low power type. The heater 185 may be controlled by the controller 170 to ensure the replacement fluid 130 is at a desired temperature when required to be used. Alternatively the heater 185 can be controlled by an independent device actuated by, for example, a pressure sensor (for example as shown at 186 in Fig. 1) triggered by the flow of fluid into the batch container 147, a timer (not shown) settable to trigger based on a predefined treatment time, or some other means. Preferably, in either case, a temperature regulator (e.g., a temperature sensor 183 combined with logic in controller 170) regulates power to the heater to ensure a required temperature is maintained and not exceeded. The temperature sensor 183 may be used to sense the quantity of filtered replacement fluid by the rate of detected temperature increase versus heater output. The temperature sensor 183, heater 185, and filtered replacement fluid 130 can be modeled in any desired fashion. For example one may neglect all but the thermal mass of the RF, assume perfect heat transfer (including assuming the RF

fluid to be isothermal). Then, the mass is given by the product of the temperature change, the thermal capacitance of the fluid, and the heat output rate of the heater. More complex theoretical or empirical algorithms would be a simple matter to derive and implement, for example the temperature variation can be fitted to the transient exponential that governs for instantaneous uniform heating from a plane source as the heater is started, taking temperature data points before substantial convection starts. The mass may also be determined by means of a contact-type pressure sensor 186 (e.g., strain gage attached to a bendable plate and calibrated against mass). Once the mass of fluid is calculated to be below a certain level, the controller 170 may be programmed to respond in accord with the assumption the filtered replacement fluid is exhausted. Equivalently, the controller 170 may simply respond to some predefined rate of temperature rise of the temperature sensor 183.

When the temperature of the filtered replacement fluid 130 is raised, dissolved gas may come out of solution. This may cause bubbles to accumulate inside the replacement fluid container 147, which is undesirable because of the risk of infusing bubbles into the patient's bloodstream. To help ameliorate that problem, a vibrator or ultrasonic transducer 184 may be provided to cause bubbles to coalesce and rise to a top of the container 147. As a result, bubble-free replacement fluid may be drawn through the outlet 148.

A connector 195 may be provided for connecting the source fluid to the line 120. The connector may be a luer, spike, threaded adapter, or

any other suitable type. Although the various controls indicated above are shown to be controlled an automatic controller 170, each may be controlled also by manual mechanisms.

The Fig. 1 embodiment allows replacement fluid to be prepared in batch for later use. Thus, the rate of filtration of replacement fluid need not match the requirements of the treatment process or preparatory steps such as priming. As a result, a low capacity filter may be used for the filter 160. For example, typically only a small quantity of expensive media is required to make a small-capacity filter and as such, the cost of a low capacity filter can be much smaller than a high capacity filter. Also, other features found in high capacity filters, such as a large ratio of media surface to volume of the filter module are achievable only by means of folding or forming media into shapes that can be difficult to manufacture, such as tubes. Thus, savings can be achieved in simplification of the configuration of the filter as well. Relatively small filters with simple planar media held in plastic casings are available and suitable for this purpose.

The configuration of Fig. 1 may be retrofitted for use with an existing treatment system. For this purpose, the outlet 148 may be provided with any required connection adapter. A user interface 175 for entering data into the controller 170 may be provided as well.

Referring now also to Fig. 2, a control algorithm for controlling the heater 185, pump 190, valves 165/180, etc. begins with the a setting of a time for treatment S10, for example by entering a

time into the controller 170 via a user interface (UI) 175. The time can be entered manually or automatically by means of, for example, a data signal from a remote source via a switched or network circuit. The time for treatment may be obtained from a treatment calendar entered into the controller 170, which also may be obtained from a remote source. In the present simple algorithm, first and second time intervals T1 and T2 are defined representing the interval required for filtration of RF and the interval required for heating of RF, respectively. These values may be obtained from any of the above means (e.g., local manual or remote entry via UI/interface 175) or from data encoded on one of the consumables involved in the process. For example, the filter 160, the RF fluid container 147, the source fluid 150 container(s), or any other consumable may be provided with one or more bar-codes, RFID tags, or other suitable encoding device. Such devices may provide values for T1 and T2, tables of values that depend upon other factors, or other data from which T1 and T2 may be derived.

The controller 170 waits until it is time to start the flow of raw RF fluid from source fluid 150 toward container 147 by comparing a current time (indicated by a clock internal to the controller 170, which is not shown) to a difference between a scheduled treatment time and T1, which represents the lead time (ahead of the scheduled treatment) required for the filtering process. A loop through step S20 is exited to step S30 when the clock reaches the treatment time minus T1. At step S30, the flow of source fluid 150 through the filter 160

is initiated. If the pump 190 is present, it may be started and regulated according to a specified TMP. The latter may be provided to the controller 170 manually or automatically through UI/interface 175. Automatic entry may be by way of a data store such as bar-code or RFID attached to the filter, for example which may be read when the filter 160 is installed in a chassis with a corresponding reader device (not shown). Note, as mentioned above, the source fluid may be sterile and the filtration process provided as a guarantee against contamination, for example by accidental touching.

Once the flow of source fluid 150 is initiated, the controller waits for the required time for applying power to the heater 185. The delay and the initiation are controlled by step S40 which is exited to step S50 only when the treatment time minus the predefined interval T2 is reached. Note that the delay may also be zero. As mentioned above, alternatively, the heater may be triggered by detecting fluid such as by means of a sensor 186 of figure 1 (not shown) triggered by the presence of filtered replacement fluid 130 in the container 147. The sensor 186 may be any of a variety of types, such as an ultrasonic sensor, capacitance sensor, mass sensor, optical sensor, etc.

Once the heater is started, the controller 170 may wait for the source fluid to be exhausted at step S60. Step S60 exits to step S70 when the source fluid is determined to be exhausted. The latter may be detected by integrating the flow rate to measure the total volume (the rate may be determined by the pumping rate, for example, or by a flow meter (not shown)). The exhaustion of the

source fluid 150 may also be indicated by a quantity indicator (e.g., a level indicator) in the filtered replacement fluid container 147 or an intermediate container supplied through a drip chamber, for example. Alternatively, the exhaustion of the source fluid 150, if supplied from a fixed-volume container, may be indicated by a sensor such as an ultrasonic sensor, capacitance sensor, mass sensor, optical sensor, a scale, etc. Yet another alternative is to sense gas or a precipitous rise in negative pressure (sensed by a pressure sensor which is not shown) at the pump 190 inlet. At step S70, the line 120 may be clamped by actuating shutoff/control valve 180. Additionally, if appropriate, the pump 190 may be deactivated at the point where the exhaustion of the source fluid 150 is detected at step S70.

According to an embodiment, as the fluid is pumped, the TMP of the filter, as indicated by pressure sensors 162, may be monitored. If the TMP is determined by the controller 170 to be, at any point, below a predetermined nominal value or to have changed precipitously during filtration, the controller 170 may trigger an alarm or take some other action to insure that the resulting replacement fluid is handled appropriately. For example, a back-up filter could be added during treatment as discussed with respect to Fig. 5. The TMP results could trigger an alarm at any point during filtration or could be assessed and reported at step S70, before treatment would begin.

The controller 170 pauses again at step S80 to wait for the sterile fluid to be exhausted. This may be indicated by a signal from the treatment

machine (e.g., received via UI/interface 175) or by direct measurement by a sensor, such as an ultrasonic sensor, capacitance sensor, mass sensor, optical sensor, a scale, etc. As mentioned above, the controller 170, or the heater 185 itself, may be provided with a threshold temperature-rise rate that indicates the mass of fluid in the replacement fluid container 147 has fallen below a minimum level. The loop of step S80 is exited to step S90 where power to the heater 185 is terminated.

Note that all the functionality of the controller 170 may be provided, via a control interface, by a controller (not shown) internal to a treatment machine. For example, the apparatus of Fig. 1 could be provided as an optional module for such a treatment machine rather than a retrofit module.

Referring now to Fig. 3, a combination blood treatment system and filtered replacement fluid device 310 has a replacement fluid preparation subsystem 305 configured substantially as the device of Fig. 1. A filter 260 filters fluid from a source of fluid 250 to generate a batch of filtered replacement fluid 230 as in the embodiment of Fig. 1. Again, the source of fluid 150 may be a container of purified or unpurified replacement fluid, one or more containers of constituents which, when combined, form a proper replacement fluid and any of the latter may include a continuous source such as a water tap. A line 320 conveys the source fluid 250 through the filter 260 and into a batch container 247, which may be any type of sterile, preferably disposable container, for example, a large IV bag. It may also include a number of such

containers appropriately interconnected to permit flow into and out of them in the fashion of container 247.

Again, a pump 290 may be provided and pressure at an outlet of the filter 260 may be sensed by a pressure sensor 262. The pump 290 may be controlled by a controller 270 to insure a maximum safe TMP to maximize throughput. Again, the pump 290 is not required and the source fluid 250 may be arranged such as to maintain a desired TMP at the filter 260 without the need of the pump 290 or pressure sensor 262 by elevation. A control valve 265 or a speed of the pump 290 may be used to regulate the flow rate to maintain desired TMP limits.

A control/shutoff valve 280 may provide the controller 270 the ability to stop the flow of fluid through the filter 260 once a desired volume is reached. A heater 285 may be provided to warm the filtered replacement fluid 230 to prepare it for use. An insulated container 245 may be used and the heater controlled using a temperature sensor 283 as discussed with respect to the Fig. 1 embodiment. Bubbles may be controlled, as discussed above, by means of a vibration or ultrasonic transducer 284 and remaining fluid by means of pressure sensor 286.

A connector 295 may be provided for connecting the source fluid to the line 320. The connector may be a luer, spike, threaded adapter, or any other suitable type. Although the various controls indicated above are shown to be controlled an automatic controller 270, each may be controlled also by manual mechanisms. Other aspects of the control mechanisms for the embodiment of Fig. 3 may

be provided as discussed with respect to Figs. 1 and 2.

The benefits of the Fig. 3 embodiment are similar to those of the Fig. 1 embodiment in that it allows replacement fluid over a time period that is not driven by the speed of supply to the treatment process. As a result, a low capacity filter may be used for the filter 260 with the attendant benefits identified above. Note that the UI/interface 275 and controller 270 are shared in the present embodiment by the treatment machine. Thus, any information required for control of both the treatment and preparation of filtered replacement fluid 230 would not need to be communicated to a separate controller such as controller 270. Note also that the communications among the illustrated components is provided by a channel 202 which may be wire harness, separate wires, a bus, a wireless channel or any suitable communications/power transmission device.

In the embodiment of Fig. 3, a predicted quantity of replacement fluid may be filtered and stored for use during treatment. If, however, for some reason, more is required, the treatment machine controller 270 could be configured to identify that situation and control the subsystem 305 components to provide it. Many blood treatment process employ a filter 220 to filter blood and into which replacement fluid is supplied to a patient 225. More details on preferred embodiments of the treatment machine are discussed below.

In either of the above embodiments, the rate of flow of fluid during preparation of the batch of replacement fluid may be substantially less

than the rate of consumption during treatment. In an exemplary embodiment of an application for hemofiltration, the amount of replacement fluid consumed is between 9 and 18 l. and the rate of consumption is approximately 200 ml./min. For daily treatment, a higher quantity of fluid is required. Also, the media used for sterile filtration may be any suitable media that insures the quality of the replacement fluid is as desired. In the embodiments discussed above, it was assumed that the end sought was preparation of filtered replacement fluid employed microfiltration to prevent the passage of pyrogens including endotoxins and any other pyrogens. However, the invention could be used with other types of filtration or treatment processes to produce a batch of fluid consumed by a medical treatment process, for example, dialysate for hemodialysis treatment. The benefits accrue in particular when the time scale of preparation may be longer than the time scale of consumption. Moreover, the benefits are more appreciable when some sort of energy-consuming process is required, such as heating, before consumption. Here, not only is the time scale of preparation compatible with a small inexpensive filter, but the long time scale permits heating of the replacement fluid over a long interval. To support this benefit, the batch container may be insulated to minimize heat loss so a small heater will be adequate. Also, the preferred application for the present invention is in the context of hemofiltration because the quantity of fluid required for such treatment is relatively small.

Note that other motivations for filtering the fluid, in addition to or as an alternative to sterilization of a non-sterile fluid, is (1) removal of air bubbles and/or (2) as a safety net for ensuring against accidental contamination. If bubble removal is the only concern, a drip chamber may be used instead of a filter. For removing bubbles, the filter preferably is of a type that permits the passage of fluid, but which blocks the passage of bubbles, for example due to its media pore size and the surface tension of the fluid.

Referring now to Fig. 4A, a preferred type of filter 400 for some of the present embodiments has an inlet port 415 providing an inlet channel 410 communicating with an inlet chamber 440. An outlet leading port 405 provides an outlet channel 420 communicating with an outlet chamber 445. A piece of filter media 425 separates the inlet and outlet chambers 440 and 445. The fluid to be sterilized enters the inlet chamber 440, is sterilized by passing through the filter media 425, and exits via the outlet chamber 445. A gas relief gasket 428 allows gas accumulating in the inlet chamber 440 to be released to the ambient atmosphere. Internal supports and structural details are not shown in the illustration for clarity, but a practical embodiment of the filter of Fig. 4 may have ribs for strength and internal supports for the media 425 and gasket 428 so that the filter 400 may be capable of tolerating a substantial TMP.

An integrated contact sensor 412 may be incorporated in the filter to sense the quality of the fluid such as its salinity. The illustration shows a pair of conductive contacts which, as will

be understood by those of skill in the art, may be connected to a conductivity measuring device to generate a signal. Note that the sensor 412 could also include a non-contact type sensor such as an induction type device.

The gas relief gasket 428 may be of a porous hydrophobic material such as PTFE. Air bubbles trapped in the inlet chamber 440 can coalesce in the inlet chamber 440 and exit via the gas relief gasket 428. It may be, depending on the type of gas relief gasket 428 used, that a substantial TMP will be required to eliminate air.

An alternative to the gas relief gasket 428 is a gas relief valve 426 as shown in Fig. 4B. Since the inlet chamber 440 is connected to the non-sterile side of the filtration system, there is little risk of contamination if microbes were to enter through a mechanical device such as the gas relief valve 426. The latter is illustrated figuratively and allows only gas to escape. Other features of the embodiment of Fig. 4B are labeled with the same numerals as features of the embodiment of Fig. 4A where they serve substantially identical functions and, thus, their descriptions are not repeated here.

Referring now to Fig. 5, the filters of Figs. 4A and 4B may be used for filtration of replacement fluid in the embodiment of Fig. 5 as discussed presently. Replacement fluid 360, which may or may not be sterile, is supplied to a hemofiltration machine 490. A replacement fluid pump 350 pumps the replacement fluid into a balancing mechanism 330 which meters the replacement fluid before it is introduced, via a junction 485,

into the venous (return) line 480 and ultimately into the blood stream of a patient 225. Note that a common alternative configuration dilutes the arterial blood at 480B before it enters the filter 395. Waste fluid is drawn through a waste line 470 from a filter 395 and pumped via a waste pump 365 through the fluid balancing mechanism 330. The fluid balancing mechanism 330 meters the replacement fluid to match the rate of withdrawal of waste fluid so that the patient's fluid balance is maintained during treatment. Actually, the rate of withdrawal of waste fluid may be greater than the rate of metering of replacement fluid by pumping waste fluid through a bypass pump called an ultrafiltration pump 339. The latter sends some of the waste fluid directly to a waste fluid sump 380, thereby bypassing the fluid balancing mechanism 330. The fluid balancing mechanism is depicted figuratively and may operate in accord with any suitable control device. Preferably it meters replacement fluid on an equal-volume or equal-mass basis. A preferred mechanism is described in US Patent Application No. 09/513,911, filed 2/25/00, entitled: "Synchronized Volumetric Fluid Balancing Systems and Methods," which is hereby incorporated by reference as if fully set forth in its entirety herein. Various sensors and line clamps, indicated figuratively at 335, 355, 320, 385, and 390, may be provided to control flow and ensure safe operation.

A filter 337, is provided in the replacement fluid line 338 just upstream of the junction 485. The filter 337 may serve as a last chance safety net for ensuring that replacement fluid is sterile and/or that all bubbles are removed

before flowing into the venous line 480. To ensure that air is not infused into the patient's body, an air sensor 390 is often provided in hemofiltration systems, but detection of air normally triggers an alarm, automatic shutdown, and skilled intervention to restart the hemofiltration treatment. Obviously, this is undesirable so the system should, as effectively as possible, insure that air or other gas is not injected into the venous line 480 without requiring interruption.

Although the embodiment of Fig. 5 includes a hemofiltration machine, other types of treatment processes may be provided a last-chance filter similar to filter 337 and air sensor 390. For example, hemodiafiltration, hemodialysis, or other treatments may require the infusion of replacement fluid and thereby benefit from a filter such as filter 337. Preferably, the filter 337 is substantially as in the embodiment of Fig. 4A. Thus, the filter 337 removes both air and pyrogens.

Instead of employing a filter at the location indicated at 337, a drip chamber may be used. Suitable drip chambers are currently available with air vents and microfilters effective to remove pyrogens, so they may be substituted for the filter 337. Also, in some cases, it may be that there is very little risk that the replacement fluid is contaminated with pyrogens, the filter 337 may serve as a mechanism for removing only air or other gases. In such cases, drip chambers which remove gas (either with or without a vent), could be employed at the above location in the fluid circuit.

Referring now to Figs. 6, 7, and 8 the last chance filter or drip chamber (or combination

device) 510 may be installed in a cartridge 520 that holds and orients blood and fluid circuits for a hemofiltration machine 540. In the embodiment shown, which is described substantially in US Patent Application No. 09/513,773 filed 2/25/00 and entitled: "Fluid Processing Systems and Methods Using Extracorporeal Fluid Flow Panels Oriented Within A Cartridge," hereby incorporated by reference in its entirety as if fully set forth herein, fluid circuit components may be held in a cartridge 520 and clamped (as shown in Fig. 8 with the machine closing as illustrated by the arrow 665) within a receiving gap 530 in a blood treatment machine such as hemofiltration machine 540. The cartridge 520 may have a preferred orientation which may insure a correct orientation for the last chance filter or drip chamber (or combination device) 510 if required by the particular device chosen. To insure orientation of the last chance filter or drip chamber (or combination device) 510, the latter is preferably held by the cartridge 520 in a fixed orientation with respect to the cartridge 520.

In an alternative embodiment, the last chance filter or drip chamber (or combination device) 520 may be accompanied by a device 660 for measuring the quality of the replacement fluid, such as conductivity or density. This may provide a last-chance check that the replacement fluid is of the correct type. For example, where such fluids are derived from mixtures, if the proportion is not exactly what is required, infusion could be harmful to the patient 225. An example of a device 660 to test the fluid could be a wettable pair of contacts (not shown) formed in a tubing set 650 of the

cartridge may be used in conjunction with a resistance measurement device to measure the ion concentration of the fluid. Alternatively, a non-wettable sensor, such as an inductive conductivity cell could be used. Other kinds of fluid quality sensors could be employed such as specific-molecule detectors built on silicon wafers and temperature sensors.

Preferably, the tubing set 650 and cartridge 620 of which it is a part form a disposable component that is used for one treatment and disposed of. Note that the fluid quality sensor 660 may used alone or together with the last chance filter or drip chamber (or combination device) 510. Note, although figures 6 and 7 are detailed, they are intended to show various components figuratively and do not reveal the details of the routing necessary to achieve the flow paths discussed with respect to them or as illustrated elsewhere.

Referring now also to Fig. 9, the tubing set and cartridge assembly 610, discussed previously, may incorporate the batch replacement fluid container 625 as part of a sterile replaceable set 690. The filter 615 may have a tube 622 with a connector 620 for attachment to a source fluid 250. A tube 635 may connect the filter to the batch replacement fluid container 625, which may be fitted with another tube 630 connected by a connector 648, which may be permanent or removable, to convey fluid to the tubing set and cartridge assembly 610. Referring now also to Fig. 10, the batch replacement fluid container 625 may also be fitted with additional connectors 670 and/or extensions (not shown) to permit the batch replacement fluid

container to be used for priming blood, replacement fluid, and/or waste lines. For example, as discussed in US Patent Application No. 09/905,246, filed 7/12/01, entitled: "Devices and Methods For Sterile Filtering of Dialysate," which is hereby incorporated by reference as if fully set forth in its entirety herein, replacement fluid is circulated through a replacement fluid container 740 to flush air out of all the fluid circuiting (not all shown) of a blood treatment apparatus 710. As described in detail in the '246 application incorporated by reference above, the venous (return) and arterial (supply) blood lines 725 and 730 may be temporarily connected via connectors 750 to the replacement fluid container 740 and fluid circulated through the container 740 until gas bubbles are substantially purged from the corresponding circuits. Note, the replacement fluid container 740 corresponds to the containers 147 (Fig. 1), 247 (Fig. 3), and 625 (Fig. 9) in the foregoing figures and to respective containers in the application incorporated by reference immediately above. The air and other gases may settle in the replacement fluid container 740 as the fluid circulates. Liberation of the gases would ordinarily be promoted by the application of heat from a heater 775 (with power source 770), which may be employed as discussed with regard to the embodiments of Figs. 1-3 or in any suitable way to bring the temperature of the replacement fluid to body temperature. Replacement fluid circuits including line 735, blood circuits including lines 725 and 730, and waste fluid circuits including line 780 may all be flushed with fluid from the container 740. The details of the

blood treatment apparatus and its internal plumbing can vary. Replacement fluid may be transferred from the replacement fluid line 735 or from the blood line 735 to the waste line, for example through a filter, to flush the waste portion of the circuit including the waste line 780. Replacement fluid may circulate through the blood circuit including lines 725 and 730 as indicated to flush the blood circuit, at least a portion of which may be closed as indicated by the arterial and venous lines 730 and 735.

Disposable components, such as the circuit sets of Figs. 8 and 9 or the batch replacement fluid container 625 alone, or other components that may be used with the embodiments disclosed may be packaged with instructions for preparing infusible replacement fluid. For example, the source fluid 150/250 or a concentrate which may be mixed to make the same (Figs. 1 and 3) may be supplied with instructions for sterile filtering the fluid as described in the instant specification. Such may constitute packages of consumables or reusable components.

Note that benefits of the filtering method and apparatus discussed above may best be achieved by performing the filtration just prior to treatment, although this is not required. The filtering method may be performed at the treatment site. For example, non-sterile concentrate may be stored at the residence of a patient. The concentrate may be diluted with distilled water in a source fluid container (e.g., 196 of Fig. 1) at the residence and processed as discussed in the instant application. Because the infusible fluid is

generated at the treatment site, the need for regulatory-cleared fluids, such as might be obtained from a manufacturer, is not avoided. Cost savings and storage-space economies can thus be realized by the patient. This is particularly important in view of the fact that renal replacement therapies are often administered many times per week and storage and cost of consumables can present a serious problem in a residence or any other facility.

Referring now to Fig. 11, a blood treatment machine, a portion of which is illustrated figuratively at 810, may permit a pump 845 that, during treatment, conveys replacement fluid to a patient, to be used for sterile filtering a non-sterile source fluid. Here, the machine 810 has a common guide 850 that accommodates a fluid line 815 through which fluid is conveyed by the pump 845, for example a peristaltic pump. During treatment, the line 815-825 may be guided by a first selected guide 830 in a first direction toward other components of an internal fluid circuit (not shown) as indicated at 825. During sterile-filtering, fluid may be pumped by the same pump 845 through a line 815-820 that is allowed to pass out of the blood treatment machine 810 via a different guide 835. This allows the line 815-820 to be fed to an external connection to the sterile fluid container (not shown) as indicated at 820.

Referring now to Figs. 12-14, a patient 640 receives a blood treatment by a continuous process performed by a blood treatment machine 610. The process extracts fluid from the blood of the patient 640 which must be replaced to prevent the patient 640 from dehydrating. For example, the

treatment process may be hemofiltration or hemodiafiltration. In such processes, blood may be drawn from the patient 640 through an access 650 and returned to the patient 640 through the same access 650.

As is known in the art, the treatment process provided by the blood treatment machine 610 may remove substantial quantities of fluids including electrolytes from the patent's 640 blood. As part of the process, as is also known, fluid may be provided to the patient 640 during treatment. During hemofiltration, for example, multiple liters of fluid may be required to replace what is withdrawn from the patient during treatment. Such fluid may require multiple standard containers 10-30 to make up a sufficient quantity to treat the patient 640.

The desired low levels of endotoxins discussed above may be provided by means of a manifold 683 having inline filters 681 on each arm 665 of the manifold 683. The manifold 683 has a header 655 connecting each arm 665 to a common feed line 645. Referring to Figures 13 and 14, filters may be located on each arm 740 of a manifold 770 as indicated at 776 or on a common feed line 790 as indicated at 779. Either embodiment may include spikes 778 or other suitable connectors for connecting to the source containers 10-30. Again, the filters 681, 776, and 779 are preferably configured to ensure levels of endotoxins in the filtered product are lower than 5 EU/Kg./hr. of treatment time and no more than 0.03 EU/ml.

Although the foregoing invention has been described by way of illustration and example, it

will be obvious that certain changes and modifications may be practiced that will still fall within the scope of the appended claims. For example, the devices and methods of each embodiment can be combined with or used in any of the other embodiments.

What is claimed is:

1. A method for performing hemofiltration, comprising the steps of:

providing at least one container of fluid that is regulatory-cleared for infusion into patients;

connecting said at least one container to at least one filter effective to ensure a concentration of endotoxins in said fluid passing therethrough is below 0.03 EU/ml;

administering to a patient a blood treatment including a step of infusing said fluid into said patient after filtering said fluid by means of said at least one filter.

2. A method as in claim 1, further comprising performing said treatment within a regulatory regime in which a standard for regulatory clearance is such that said fluid may contain more than 0.03 EU/ml.

3. A method as in claim 1, wherein said step of administering includes drawing said fluid from said at least one container and passing it through said at least one filter, whereby said fluid is filtered as it is consumed by said treatment.

4. A method as in claim 1, wherein said at least one filter is located immediately upstream of a flow junction at which said fluid is injected into a venous line returning blood into said patient.

5. A method as in claim 1, wherein said at least one filter is effective to reduce a concentration of endotoxins in said fluid such as to deliver no more than 5 EU/hr per Kg of patient weight of fluid upon filtration thereof at a defined rate of infusion into said patient.

6. A method as in claim 1, wherein at least one container is at least two containers and said at

least one filter is at least one filter for each of said containers, each said filtering being connected inline in a respective flow line connected to each of said at least two containers, whereby fluid from each container is filtered by its own filter.

7. A method as in claim 1, wherein:

said at least one filter is at least two;

said step of administering includes drawing said fluid from said at least one container and passing it through at least one of said at least two filters, whereby said fluid is filtered as it is consumed by said treatment; and

at least another of said at least two filters is located upstream of a flow junction at which said fluid is injected into a venous line returning blood into said patient such that said fluid is double-filtered before entering said patient's body.

8. A method as in claim 7. wherein said at least another of said at least two filters is located immediately upstream of said flow junction at which said fluid is injected into said venous line.

9. A method for performing hemofiltration, comprising the steps of:

providing at least one container of fluid that is regulatory-cleared for a defined rate of infusion into patients;

connecting said at least one container to at least one filter effective to reduce a concentration of endotoxins in said fluid to a rate below that of said fluid in said container;

administering to a patient a blood treatment including a step of infusing said fluid

into said patient at said defined rate after filtering said fluid by means of said at least one filter.

10. A method as in claim 9, further comprising performing said treatment within a regulatory regime in which a standard for regulatory clearance for said defined rate of infusion is such that said fluid may contain more than 0.03 EU/ml.

11. A method as in claim 9, wherein said step of administering includes drawing said fluid from said at least one container and passing it through said at least one filter, whereby said fluid is filtered as it is consumed by said treatment.

12. A method as in claim 9, wherein said at least one filter is located immediately upstream of a flow junction at which said fluid is injected into a venous line returning blood into said patient.

13. A method as in claim 9, wherein said at least one filter is effective to reduce a concentration of endotoxins in said fluid to such as to deliver to a patient no more than 5 EU/hr per Kg. of patient weight of fluid upon filtration thereof at said defined rate of infusion.

14. A method as in claim 9, wherein at least one container is at least two containers and said at least one filter is at least one filter for each of said containers, each said filtering being connected inline in a respective flow line connected to each of said at least two containers, whereby fluid from each container is filtered by its own filter.

15. A method as in claim 9, wherein:

said at least one filter is at least two;

said step of administering includes drawing said fluid from said at least one container and

passing it through at least one of said at least two filters, whereby said fluid is filtered as it is consumed by said treatment; and

at least another of said at least two filters is located upstream of a flow junction at which said fluid is injected into a venous line returning blood into said patient such that said fluid is double-filtered before entering said patient's body.

16. A method as in claim 15. wherein said at least another of said at least two filters is located immediately upstream of said flow junction at which said fluid is injected into said venous line.

17. A method as in claim 9, wherein said at least one filter is effective to reduce a concentration of endotoxins in said fluid to a rate below 0.03 EU/ml.

18. A method for performing hemofiltration, comprising the steps of:

providing at least one container of fluid for infusion into patients;

connecting said at least one container to at least one filter effective to ensure a concentration of endotoxins in said fluid passing therethrough is below both 0.03 EU/ml and such as to deliver no more than 5 EU/hr per Kg of patient weight at a defined rate of infusion into a patient;

administering to a patient a blood treatment including a step of infusing said fluid into said patient.

19. A method as in claim 18, further comprising performing said treatment within a regulatory regime in which a standard for regulatory clearance for

said defined rate of infusion is such that said fluid may contain more than 0.03 EU/ml.

20. A method as in claim 18, wherein said step of administering includes drawing said fluid from said at least one container and passing it through said at least one filter, whereby said fluid is filtered as it is consumed by said treatment.

21. A method as in claim 18, wherein said at least one filter is located immediately upstream of a flow junction at which said fluid is injected into a venous line returning blood into said patient.

22. A method as in claim 18, wherein said at least one filter is effective to reduce a concentration of endotoxins in said fluid to a rate such as to deliver to said patient no more than 5 EU/hr. per Kg. of patient weight of fluid upon filtration thereof at said defined rate of infusion into said patient.

23. A method as in claim 18, wherein at least one container is at least two containers and said at least one filter is at least one filter for each of said containers, each said filtering being connected inline in a respective flow line connected to each of said at least two containers, whereby fluid from each container is filtered by its own filter.

24. A method as in claim 18, wherein:

said at least one filter is at least two;

said step of administering includes drawing said fluid from said at least one container and passing it through at least one of said at least two filters, whereby said fluid is filtered as it is consumed by said treatment; and

at least another of said at least two filters is located upstream of a flow junction at which said

fluid is injected into a venous line returning blood into said patient such that said fluid is double-filtered before entering said patient's body.

25. A method as in claim 24, wherein said at least another of said at least two filters is located immediately upstream of said flow junction at which said fluid is injected into said venous line.

26. A method as in claim 18, wherein said at least one filter is effective to reduce a concentration of endotoxins in said fluid to a rate below 0.03 EU/ml.

27. A method for performing hemofiltration, comprising the steps of:

filtering a replacement fluid to ensure against a presence of endotoxins, in a filtered fluid resulting from said step of filtering, at a concentration no higher than 0.03 EU/ml;

drawing a waste fluid from a patient;

infusing said filtered fluid into said patient;

said step of filtering including filtering with a media having a pore size that is ineffective to block endotoxins, but made of a material that is effective to adsorb endotoxins.

28. A method as in claim 27, further comprising performing said treatment within a regulatory regime in which a standard for regulatory clearance for said defined rate of infusion is such that said fluid may contain more than 0.03 EU/ml.

29. A method as in claim 27, wherein said step of administering includes drawing said fluid from said at least one container and passing it through

said at least one filter, whereby said fluid is filtered as it is consumed by said treatment.

30. A method as in claim 27, wherein said at least one filter is located immediately upstream of a flow junction at which said fluid is injected into a venous line returning blood into said patient.

31. A method as in claim 27, wherein said at least one filter is effective to reduce a concentration of endotoxins in said fluid to a rate such as to deliver to said patient no more than 5 EU/hr per Kg. of patient weight of fluid upon filtration thereof at said defined rate of infusion into said patient.

32. A method as in claim 27, wherein at least one container is at least two containers and said at least one filter is at least one filter for each of said containers, each said filtering being connected inline in a respective flow line connected to each of said at least two containers, whereby fluid from each container is filtered by its own filter.

33. A method as in claim 27, wherein:

said at least one filter is at least two;

said step of administering includes drawing said fluid from said at least one container and passing it through at least one of said at least two filters, whereby said fluid is filtered as it is consumed by said treatment; and

at least another of said at least two filters is located upstream of a flow junction at which said fluid is injected into a venous line returning blood into said patient such that said fluid is double-filtered before entering said patient's body.

34. A method as in claim 33, wherein said at least another of said at least two filters is located immediately upstream of said flow junction at which said fluid is injected into said venous line.

35. A method as in claim 27, wherein said at least one filter is effective to reduce a concentration of endotoxins in said fluid to a rate below 0.03 EU/ml.

36. A device for performing hemofiltration, comprising:

at least one container of fluid for infusion into patients;

connected to said at least one container, at least one filter effective to ensure a concentration of endotoxins in said fluid passing therethrough is below both 0.03 EU/ml and such as to deliver no more than 5 EU/hr per Kg of patient weight at a defined rate of infusion into a patient;

a hemofiltration system including at least one pump for pumping blood from and back to said patient;

a fluid circuit for conveying said blood, said fluid circuit connecting an outlet of said filter with a return flow of blood, whereby replacement fluid having a low level of pyrogens in infused into said patient.

37. A device as in claim 36, wherein said at least one filter is at least two, each of which is incorporated in an inline configuration in a respective arm of a manifold.

38. A device as in claim 36, wherein said at least one filter includes a membrane of charged nylon.

39. A device as in claim 36, wherein said at least one filter includes filter medium being such that an endotoxin load of a filtrate thereof is obtained by a combination of mechanical blocking due to small pore size and adsorption, whereby a pressure drop of said medium is lower than would be required if the medium relied on pore size alone to reduce the endotoxin load to said concentration.

40. A disposable fluid circuit for infusion, comprising:

a line for receiving an infusible fluid;

a pumping portion for engagement with a peristaltic pump;

an inline filter downstream of said pumping portion and immediately prior to a connector to a patient access configured to filter an infusate prior to contact with a patient blood stream;

said inline filter having properties to one of degass and reduce a rate of endotoxins of said infusate.

41. A fluid circuit as in claim 40, wherein said fluid circuit includes a blood filter or dialyzer and said inline filter is located immediately upstream of a junction for diluting blood.

42. A fluid circuit as in claim 41, wherein said inline filter is configured to reduce a rate of endotoxins to 3 EU/ml. or less.

43. A fluid circuit as in claim 40, further comprising a portion for engagement with an air sensor downstream of said inline filter.

44. A fluid circuit as in claim 43, wherein said inline filter is configured to reduce a rate of endotoxins to 3 EU/ml. or less.

45. A fluid circuit as in claim 40, further comprising fluid property detection sensor.

46. A fluid circuit as in claim 45, wherein said fluid property detection device includes a conductivity detector.

47. A disposable fluid circuit for infusion, comprising:

a line for receiving an infusible fluid;

a pumping portion for engagement with a peristaltic pump;

an inline sensor effective to detect a property of an infusate prior to contact with a patient blood stream.

48. A fluid circuit as in claim 46, wherein said inline sensor includes at least a portion of a conductivity cell.

49. A fluid circuit as in claim 47, wherein said inline sensor is integrated within the housing of an inline filter that is arranged to filter said infusate.

50. A disposable fluid circuit for renal replacement therapy and connectable with a blood treatment machine, comprising:

a blood line connectable to a blood filter having properties appropriate for treatment by hemofiltration or dialysis;

said blood line having arterial and venous portions connectable to a patient access;

a replacement fluid line connected to said venous portion of said blood line for diluting blood;

a connection for an inline component in said replacement fluid line located immediately upstream

of a junction joining said replacement fluid line and said venous portion;

said inline component including at least one of an inline filter effective to block pyrogens and/or air and a fluid property sensor connectable to a controller or alarm.

51. A fluid circuit as in claim 50, wherein said inline component includes a sterile filter permanently connected to said connection.

52. A fluid circuit as in claim 51, wherein said inline component includes an inline filter with media capable of reducing a rate of endotoxins to less than 3 EU/ml.

53. A fluid circuit as in claim 52, wherein said inline filter is permanently connected to said replacement fluid line.

54. A fluid circuit as in claim 53, wherein said inline filter includes media capable of blocking gas bubbles.

55. A fluid circuit as in claim 54, further comprising a cartridge for supporting said replacement fluid line, said blood line, and said inline filter, said cartridge engaging with said blood treatment machine to orient it with respect thereto.

56. A fluid circuit as in claim 55, wherein said inline filter is operable in a selected orientation and said cartridge orients said inline filter when said cartridge is engaged with said blood treatment machine.

57. A fluid circuit as in claim 56, wherein said inline filter includes media capable of reducing a rate of endotoxins to less than 3 EU/ml.

58. A fluid circuit as in claim 54, further comprising a portion for engagement with an air detector downstream of said inline filter.

59. A fluid circuit as in claim 54, further comprising a cartridge for supporting said replacement fluid line, said blood line, and said inline filter, said cartridge engaging with said blood treatment machine to orient it with respect thereto.

60. A fluid circuit as in claim 55, wherein said inline filter is operable in a selected orientation and said cartridge orients said inline filter when said cartridge is engaged with said blood treatment machine.

61. A fluid circuit as in claim 50, wherein said blood treatment machine is a hemofiltration machine.

62. A fluid circuit as in claim 61, wherein said inline component includes an inline filter with media capable of reducing a rate of endotoxins to less than 3 EU/ml.

63. A fluid circuit as in claim 50, wherein said blood line is permanently connected to said blood filter.

64. A fluid circuit as in claim 50, further comprising a connection connectable to a source of sterile replacement fluid and wherein said inline component includes an inline filter with media capable of reducing a rate of endotoxins to less than 3 EU/ml.

65. A device for batch preparation of replacement fluid retrofittable to a blood treatment machine, comprising:

a disposable fluid circuit including a replacement fluid container with a first input line having a connector for an inline sterile filter and an inlet connectable to a source of replacement fluid to be filtered by said sterile filter;

a peristaltic pump actuator;

said first input line having a pumping portion engageable with said peristaltic pump actuator;

said replacement fluid container having a first outlet connectable to a replacement fluid connector of a blood treatment machine that consumes replacement fluid in performing renal replacement therapy.

66. A device as in claim 65, further comprising an insulated housing for supporting said replacement fluid container.

67. A device as in claim 66, further comprising a heater for warming said replacement fluid container.

68. A device as in claim 67, further comprising a controller configured to regulate a temperature of said replacement fluid container.

69. A device as in claim 65, further comprising a control valve and a controller configured to shut said control valve after a quantity of replacement fluid is filtered by said filter.

70. A device as in claim 65, further comprising a heater to heat filtered replacement fluid and a controller configured to control said pump and said heater responsively to a scheduled treatment time.

71. A device as in claim 65, wherein said controller is configured to filter said replacement fluid at a time such that a batch of replacement fluid is filtered, stored in said replacement fluid

container, and heated to a specified temperature immediately prior to said scheduled treatment time.

72. A device as in claim 65, wherein said controller is configured to filter said replacement fluid and maintain a temperature thereof until a time for consumption by said blood treatment machine.

73. A tubing set for preparation of replacement fluid by sterile filtering, comprising:

a sterile replacement fluid container with an inlet line connected to a filter and a connector for drawing replacement fluid from a source;

an outlet port for drawing filtered replacement fluid from said replacement fluid container;

at least one recirculation port to flow sterile replacement fluid in a recirculating flow through said replacement fluid container to purge air from said outlet line, said recirculation port and a connection between them provided by a blood treatment circuit.

74. A set as in claim 73, wherein said filter contains media capable of reducing a rate of endotoxins to less than 3 EU/ml.

75. A set as in claim 73, wherein said outlet port is connected to an outlet line having connector.

76. A set as in claim 73, wherein said at least one is at least two ports.

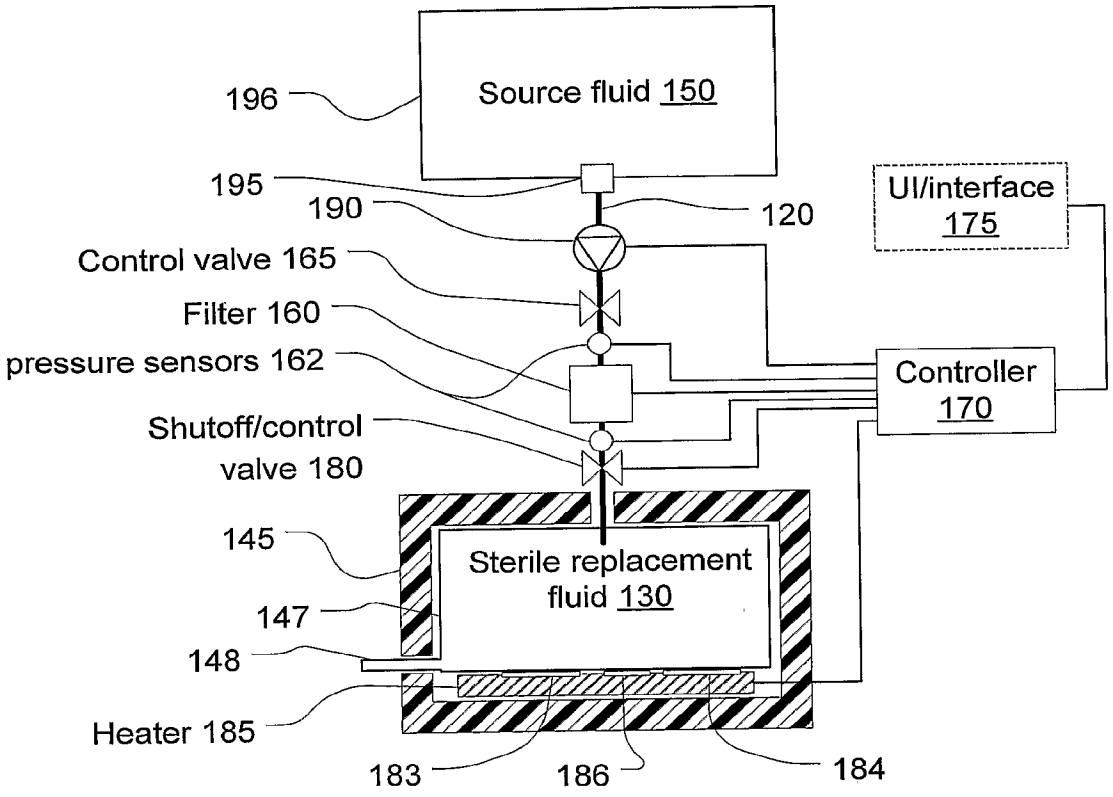

Fig. 1

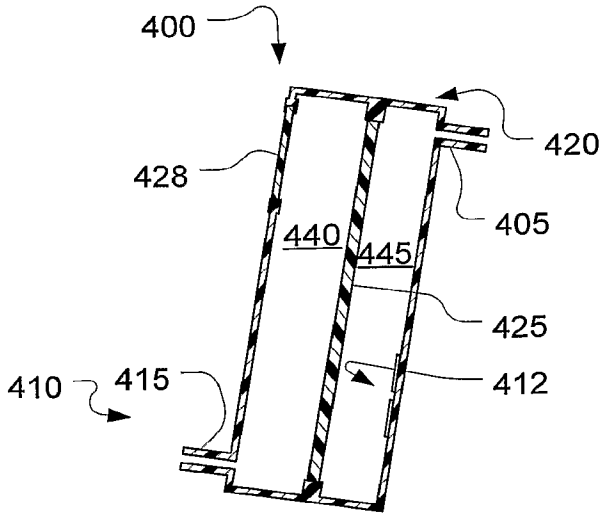

Fig. 4A

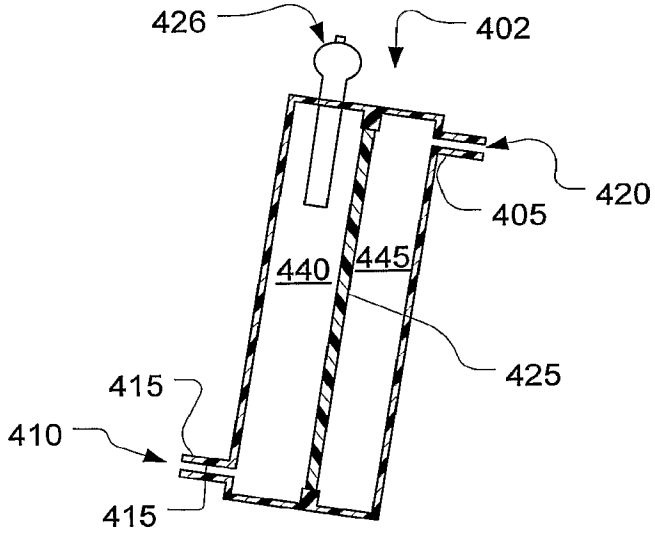

Fig. 4B

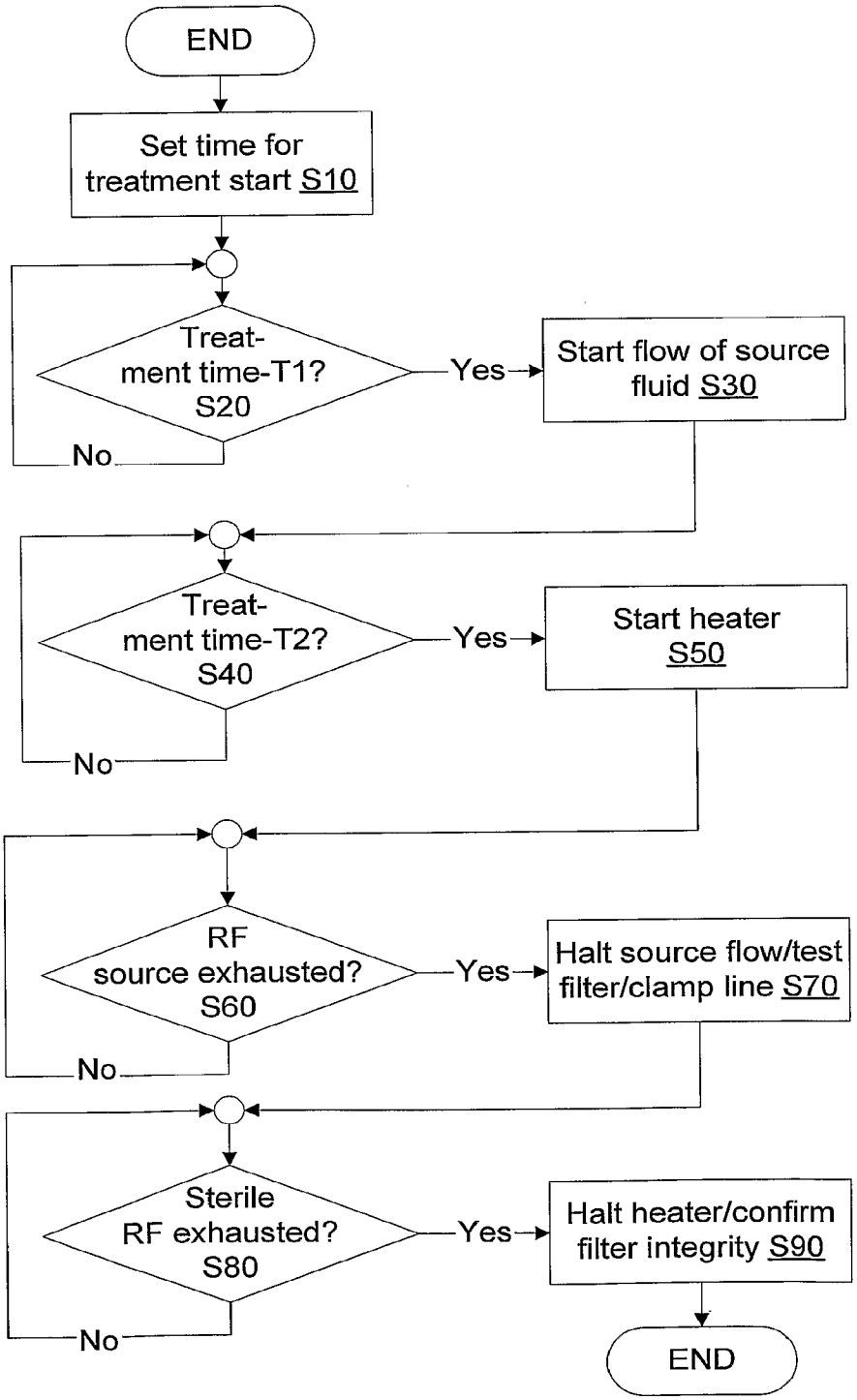
END
Set time for treatment start S10
Treat-ment time-T1? S20
Yes
No
Start flow of source fluid S30
Treat-ment time-T2? S40
Yes
No
Start heater S50
RF source exhausted? S60
Yes
No
Halt source flow/test filter/clamp line S70
Sterile RF exhausted? S80
Yes
No
Halt heater/confirm filter integrity S90
END

Fig. 2

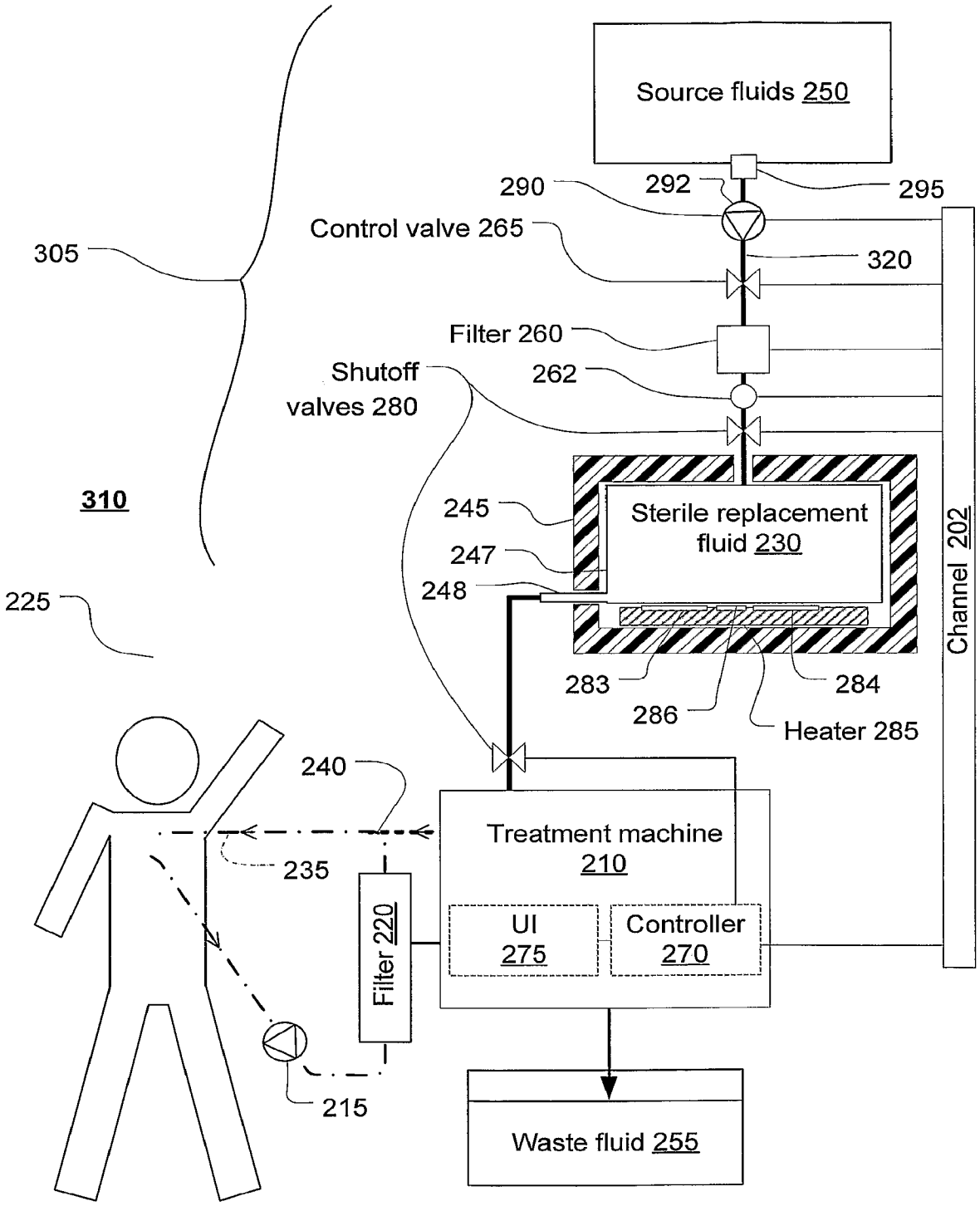
Source fluids 250
290
292
295
Control valve 265
305
320
Filter 260
Shutoff valves 280
262
310
245
Sterile replacement fluid 230
247
248
225
Channel 202
283
284
286
Heater 285
240
Treatment machine 210
235
UI 275
Controller 270
Filter 220
215
Waste fluid 255

Fig. 3

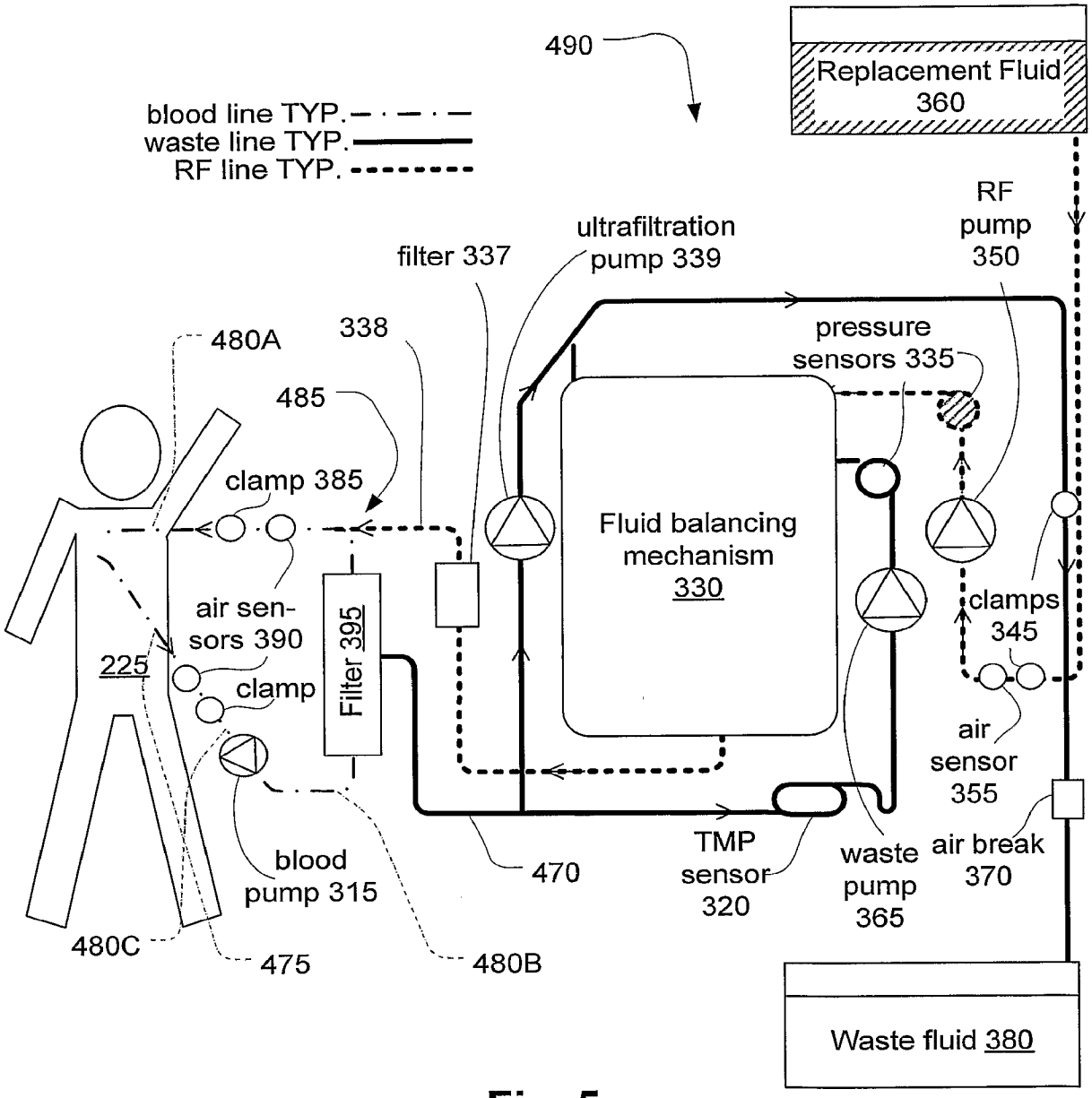
490
Replacement Fluid 360
blood line TYP.
waste line TYP.
RF line TYP.
RF pump 350
ultrafiltration pump 339
filter 337
338
480A
485
pressure sensors 335
clamp 385
Fluid balancing mechanism 330
air sensors 390
225
clamp
Filter 395
clamps 345
air sensor 355
blood pump 315
470
TMP sensor 320
waste pump 365
air break 370
480C
475
480B
Waste fluid 380

Fig. 5

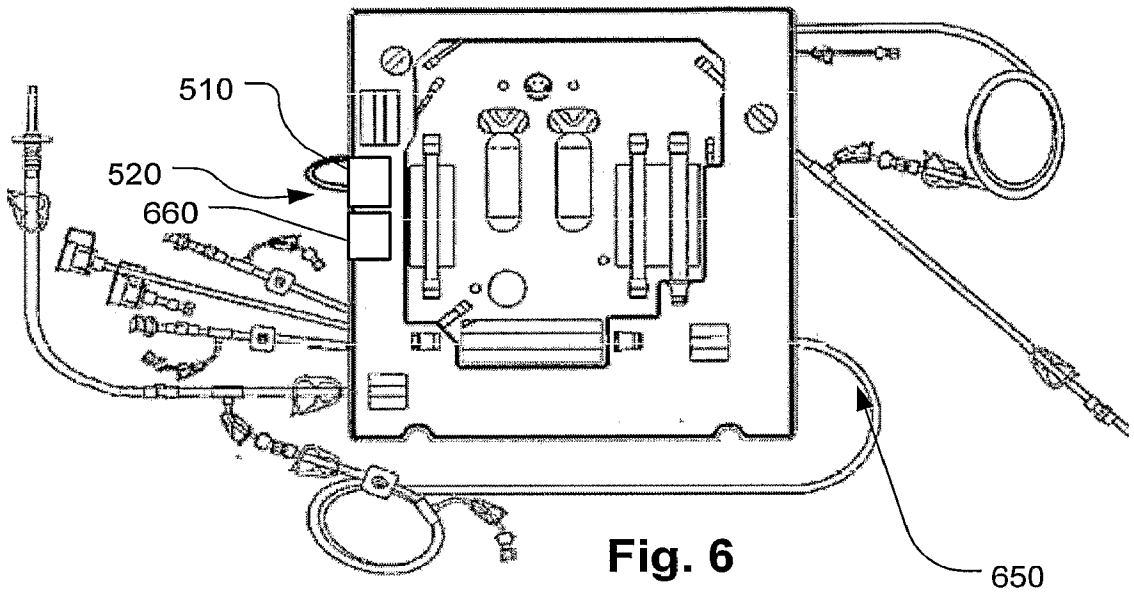

Fig. 6

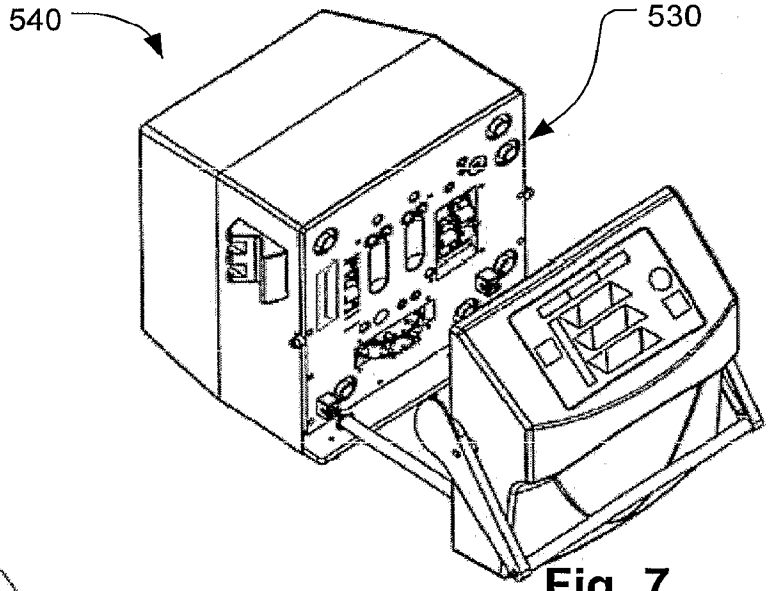

Fig. 7

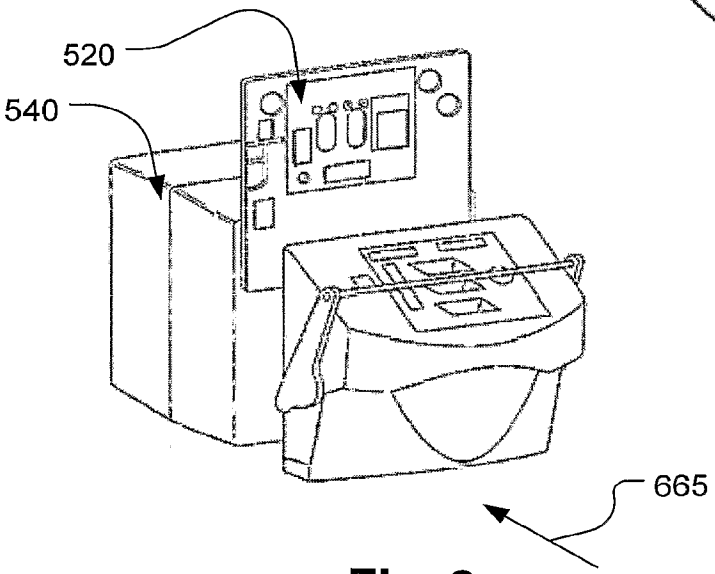

Fig. 8

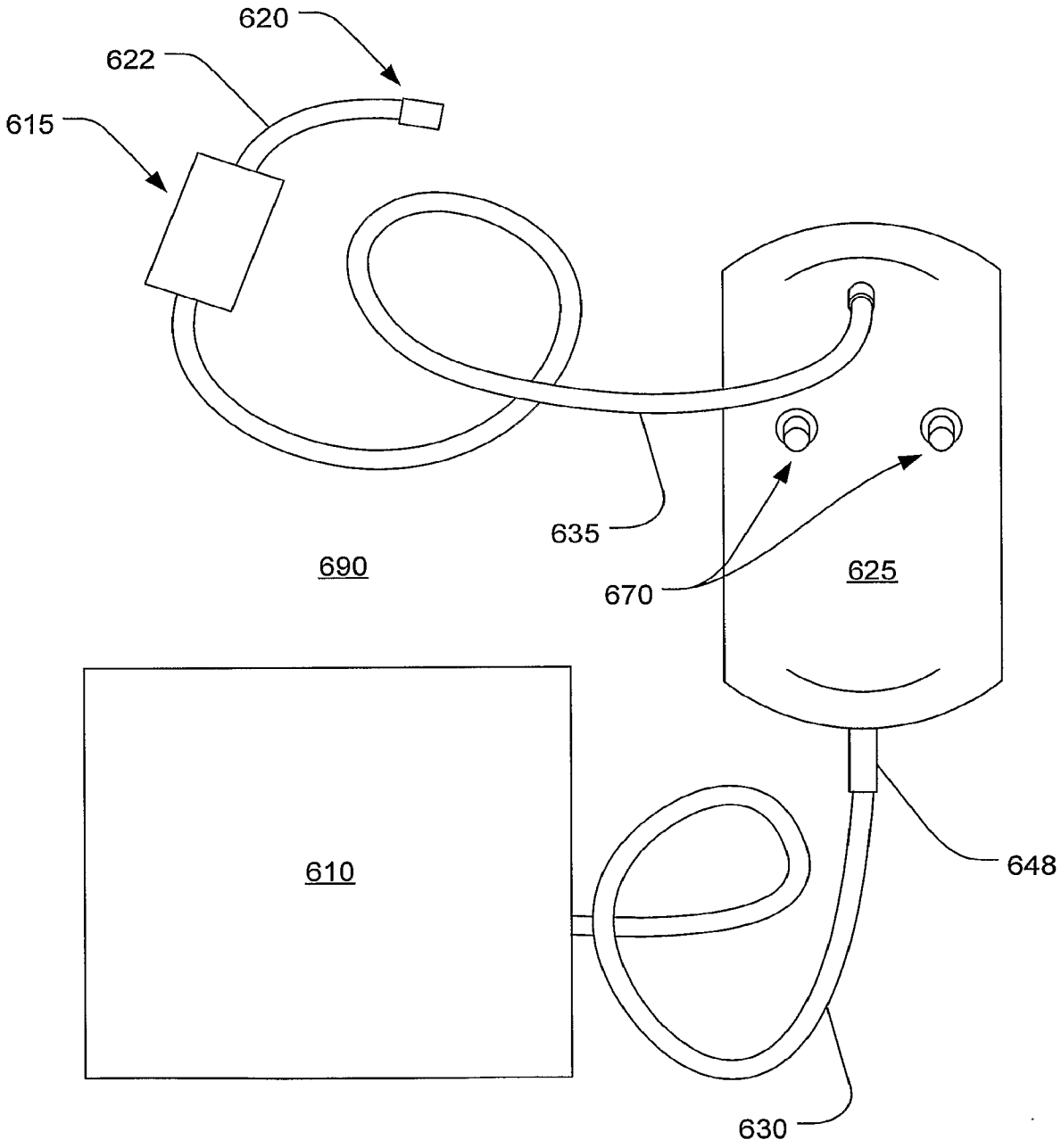

Fig. 9

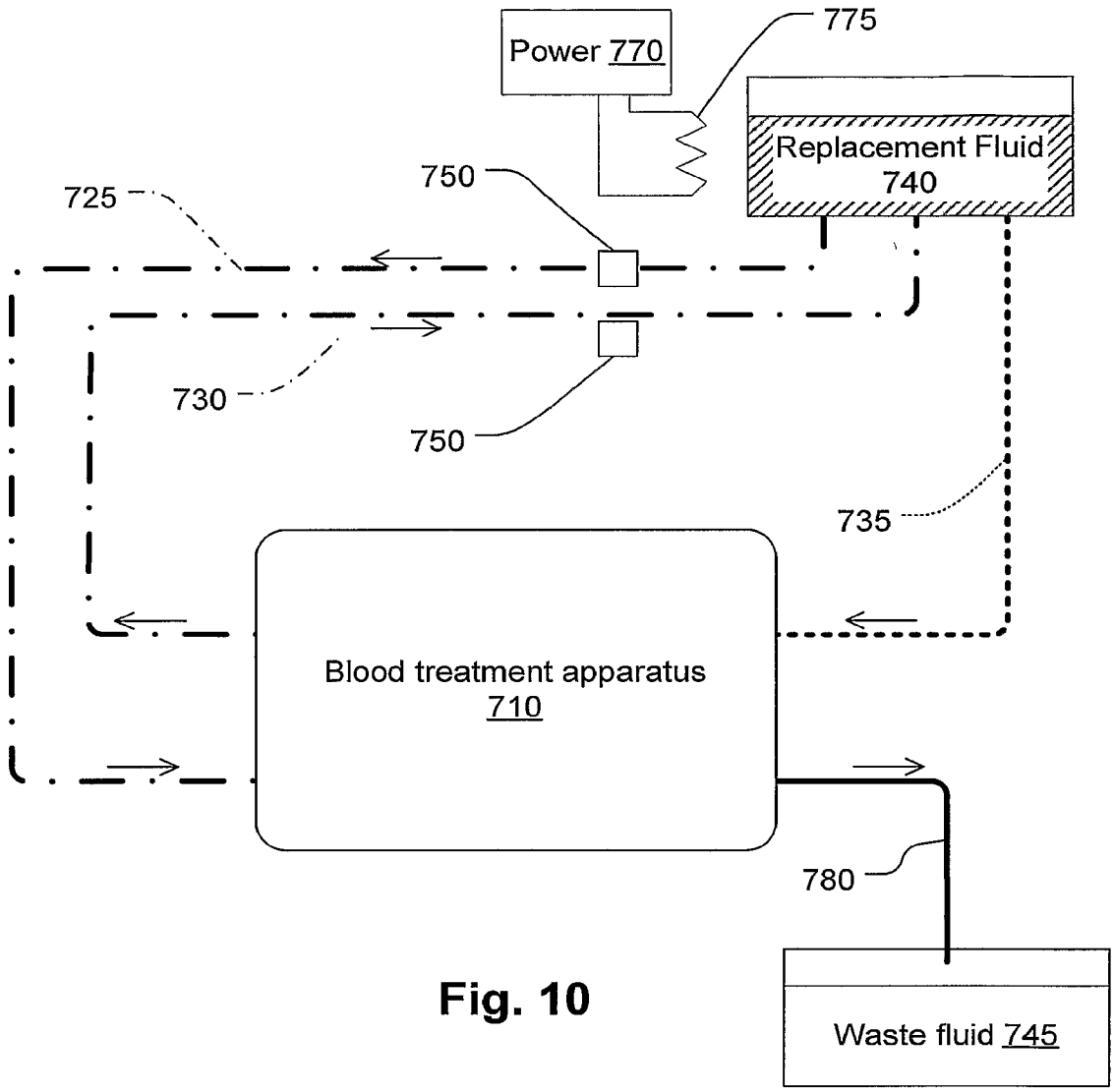
Power 770
775
Replacement Fluid
740
750
725
730
750
735
Blood treatment apparatus
710
780
Waste fluid 745

Fig. 10

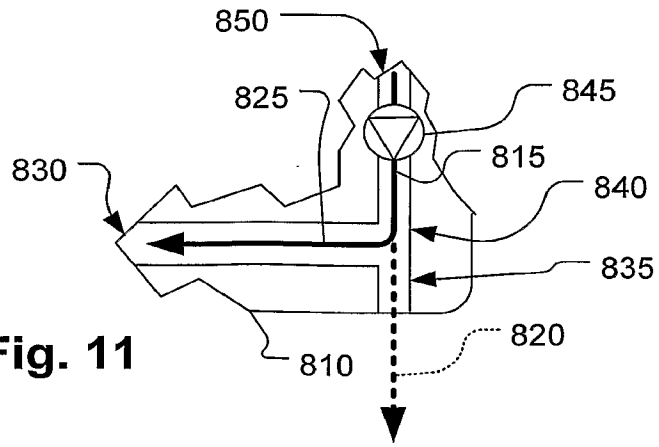
850
825
845
815
830
840
835
820
810

Fig. 11

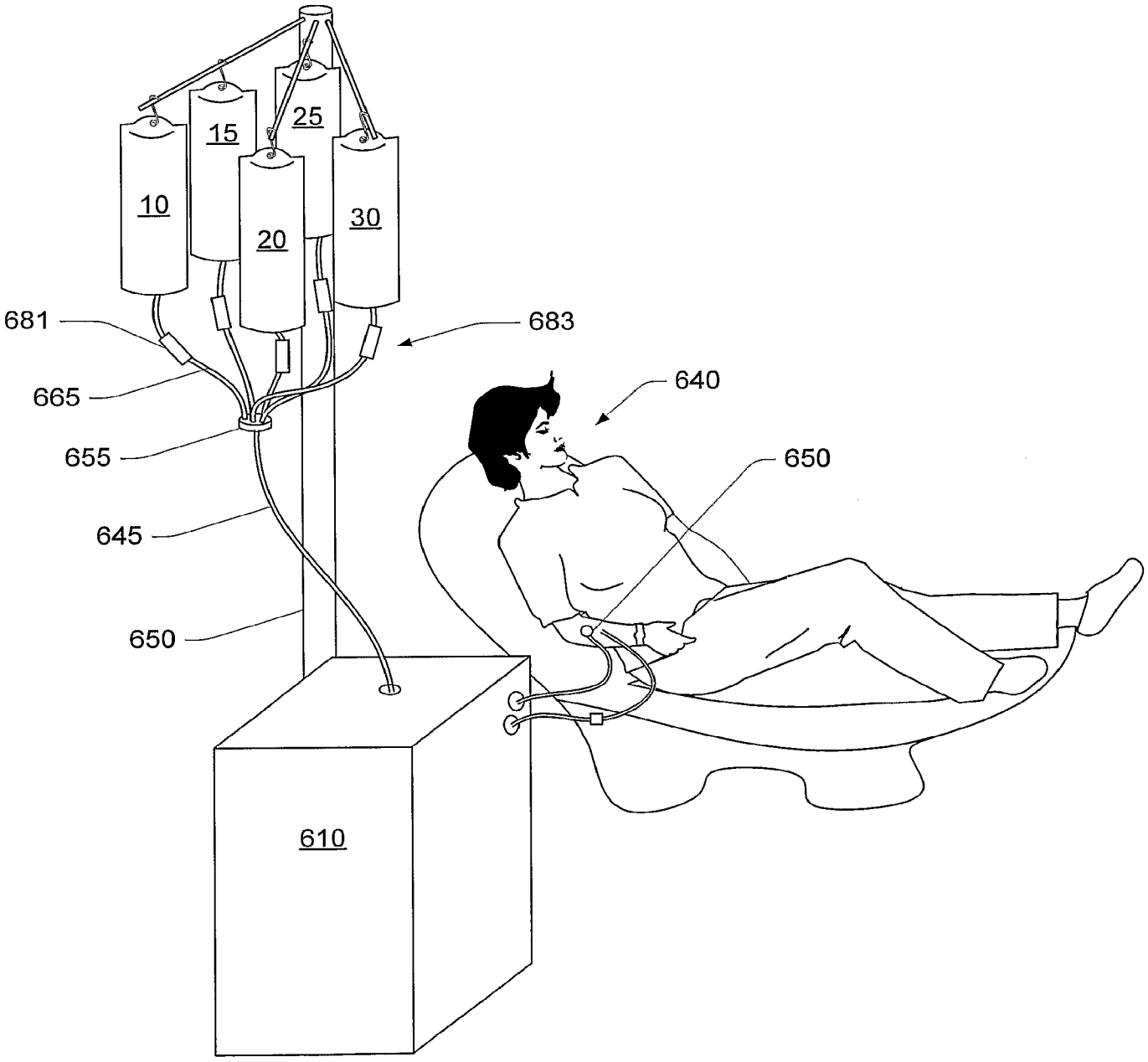

Fig. 12

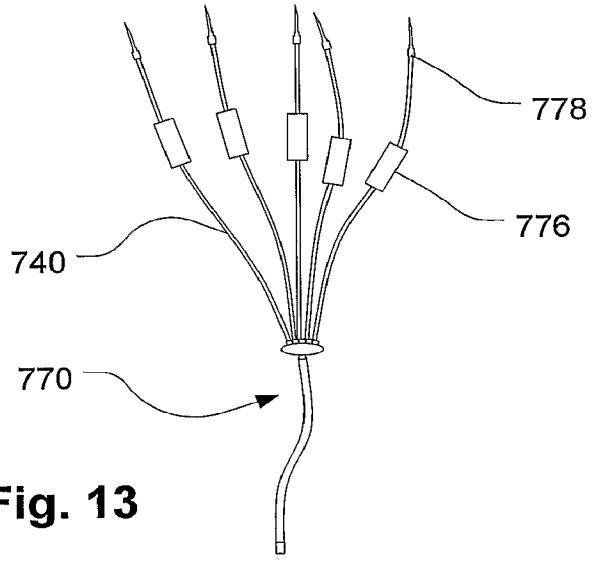

Fig. 13

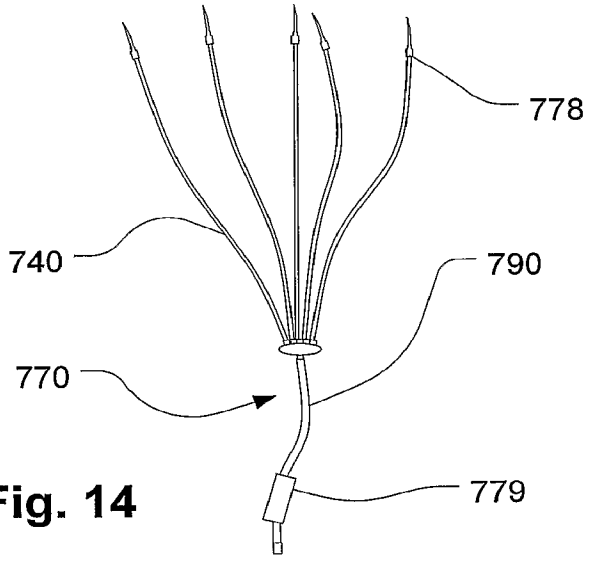

Fig. 14